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**New drug controls and reduced hospital presentations due to novel psychoactive substances in
Edinburgh**

Short: Public health interventions for NPS toxicity

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25 **ABSTRACT**

26

27 **Aims:** Recreational use of novel psychoactive substance (NPS) has become increasingly common. We
28 aimed to assess the association of national legislation and local trading standards activity with hospital
29 presentations.

30 **Methods:** We established observational cohorts of patients with recreational drug toxicity presenting to
31 Edinburgh Royal Infirmary and dying with detectable recreational drugs in Edinburgh. We assessed
32 associations with two temporary class drug-orders (TCDO, Apr 2015: methylphenidates, Nov 2015:
33 methiopropamine), the Psychoactive Substances Act (Jun 2016), and trading standards forfeiture
34 orders (Oct 2015).

35 **Results:** The methylphenidate TCDO was associated with rapid 46.7% ($p=0.002$) and 21.0% ($p=0.003$)
36 reductions in presentations and admissions, respectively, for NPS drug toxicity, comparing 12-months
37 before with 6-months after. The change was greatest for ethylphenidate toxicity (96.7% reduction in
38 admissions, $p<0.001$) that was partly offset by a tripling in synthetic cannabinoid receptor agonist
39 (SCRA) cases ($p<0.001$) over the next 6-months. This increase reversed following trading standards
40 activity removing all NPS drugs from local shops in Oct 2015, associated with 64.3% ($p<0.001$) and
41 83.7% ($p<0.001$) reductions in presentations and admissions, respectively, for all NPS drugs over the
42 next 12-months. The effect was sustained and associated with a reduced detection of stimulant NPS
43 drugs in post-mortems. The two interventions prevented an estimated 557 (95%CI 327-934) NPS
44 admissions during 2016, saving an estimated £303,030 (£177,901-£508,133) in hospital costs.

45 **Conclusions:** We show here that drug legislation and trading standards activity may be associated
46 with effective and sustained prevention. Widespread adoption of trading standards enforcement,
47 together with focused legislation, may turn the tide against these highly-damaging drugs.

48

49 **Keywords:**

WHAT THIS PAPER ADDS

1. What is already known on this subject.

- The use of novel psychoactive substances (NPS, 'legal highs') as recreational drugs is a major source of drug harm in the UK.
- The government has used temporary control orders (TCDOs) and more recently the Psychoactive Substances Act to control their use and the harms; local councils have used trading standard actions to prevent shops selling NPS.
- There is currently little evidence on the effect of these interventions on NPS induced harm and switching to other drugs

Section 2: What this study adds.

- This study shows that the ethylphenidate TCDO was associated with an almost complete disappearance of admissions with reported ethylphenidate toxicity
- Subsequent trading standards activity, removing all NPS from local shops, was associated with a sustained > 80% reduction in NPS admissions to hospital over the next year.
- Such a combined approach, spread across the UK, could offer major health benefits and save the health service millions of pounds per year.

72 **INTRODUCTION**

73

74 The use of novel psychoactive substances (NPS), sometimes previously referred to as 'legal highs', is a
75 recent phenomenon in the UK and worldwide [1-3]. NPS drugs are commonly stimulants (based on an
76 amphetamine structure) [4, 5], highly potent synthetic cannabinoid receptor agonists (SCRA) [5, 6], or
77 novel high potency benzodiazepines such as diclazepam or etizolam [7, 8]. They are bought online or
78 from high street 'head shops', sometimes sold as research chemicals labelled 'not for human
79 consumption' [2, 3], or as common illicit drugs. Serious complications and deaths can occur [9].
80 Stimulants can cause agitation, seizures, hyperthermia and rarely multiorgan failure [4, 10], while
81 SCRA can cause tachycardia, agitation, psychosis, and rarely stroke, seizures, myocardial infarction,
82 or rhabdomyolysis [6, 10], and novel benzodiazepines cause coma & respiratory arrest at low doses [8].

83

84 Most NPS were not controlled by the Misuse of Drugs Act (1971). Instead, piecemeal and temporary
85 actions (reclassifications and temporary class drug orders [TCDOs]) were enacted to control specific
86 substances or classes [11]. Such actions, both in the UK and overseas, have been associated with
87 reductions in use [9, 12]. However, reported studies have been of poor design and the overall evidence
88 for effect from interventions is weak [12]. Furthermore, NPS producers have usually stayed ahead of
89 these actions by making minor revisions of chemical structure, creating new uncontrolled compounds
90 [9, 13, 14]. In response, the UK government enacted legislation in May 2016 that specifically addressed
91 this problem by controlling all psychoactive substances, regardless of chemical structure [Psychoactive
92 Substances Act (2016)] [15]. The effectiveness of this intervention is uncertain.

93

94 Edinburgh has been affected by multiple waves of NPS toxicity over the last eight years, from
95 mephedrone in 2009 [16], to desoxypipradrol in 2010 [17], to ethylphenidate in 2014. Ethylphenidate
96 was a particular problem, causing a marked increase in deaths, hospital admissions, and complications

(including severe agitation, psychosis, abscesses, skin ulcers, & endocarditis), often in people who previously used heroin [18-20]. To investigate the impact of legislative and local trading standards actions on NPS associated harms, we report on the number of patients presenting and being admitted to the specialist toxicology ward in Edinburgh.

METHODS

Anonymous data for audit of management of recreational drug toxicity are routinely and prospectively collected on a secure database held within the clinical toxicology unit of the Royal Infirmary of Edinburgh. Data on patients presenting to the Emergency Departments and discharged, without admission to the toxicology units, were also recorded. The use of these anonymous unlinked databases for audit has approval of the data protection officer/Caldicott Guardian of NHS Lothian Health Board. Toxicology data on fatalities is generated and stored by the Department of Forensic Medicine and Science, University of Glasgow, on behalf of the Crown Office and Procurator Fiscal Service. Interrogation of this data was approved by the West of Scotland NHS REC (17/WS/0037).

Patient involvement

Patients were not involved in formulating the research question or in designing and conducting the research.

Hospital presentations and admissions

Consecutive patients presenting to the emergency department of the Royal Infirmary of Edinburgh with a history of recreational drug toxicity over 33 months, from 1 April 2014 until 31 December 2016, were included in this study. Patients who took recreational drugs for self-harm were excluded. Patients admitted to the toxicology ward or other hospital wards, including the intensive care unit, were seen by

the toxicology nursing and medical staff and their data prospectively recorded. Patients discharged from the emergency department, without admission, were identified by retrospective review of medical notes. Data were entered into a standard database.

For admitted patients, the drugs were identified by toxicology staff, based on careful questioning about history as well as the toxidrome produced. They were grouped into the following categories: NPS, conventional opioids, conventional stimulants (including amphetamine, metamphetamine, MDMA, and cocaine), non-NPS benzodiazepines, and 'other' recreational drugs (including ketamine, GHB, GBL, cannabis, gabapentin and pregabalin). NPS drugs were sub-divided into reported ethylphenidate, other stimulant (not identified as ethylphenidate), SCRA, sedative (likely benzodiazepines), hallucinogenic, or 'unknown' groups, based on history and local epidemiology (from both drug seizures and laboratory analysis) [10]. Urine toxicology screens were not routinely done. For patients discharged without admission, the drug was identified through retrospective review of the notes.

Fatal cases

All sudden, unexplained or suspicious deaths in Scotland are investigated by the Crown Office and Procurator Fiscal Service. Where appropriate, this includes toxicological analysis of blood and urine samples for a broad spectrum of drugs including NPS, carried out by the department of Forensic Medicine and Science at the University of Glasgow. All cases were tested for alcohol and underwent an ELISA based classic drugs of abuse screen and GCMS (with a mixed-mode solid phase extraction) analysis for: 1) drugs of abuse initially identified by ELISA, 2) ten benzodiazepines (including etizolam and phenazepam), 3) paracetamol, and 4) a drugs screen including around 61 known compounds, both prescribed and illicit. Unknowns picked up by GCMS were compared with a library of compounds for identification. Where there was prior intelligence (for example if specific drugs were found at the scene or common local use of a particular NPS was identified [eg. ethylphenidate [19]]), further focused testing

was included. Due to the wide variation of chemical characteristics of drugs and their changing availability it was not possible to test every case for every drug; however, each case was reviewed individually to ensure all relevant tests were included.

Anonymised data were collected for all deaths with detectable recreational drugs in the Edinburgh fiscal area (covering the City of Edinburgh and its suburbs). Many cases showed poly-drug use.

Interventions

Five public health measures were implemented during the study period to curb the availability of NPS. On 10 April 2015, five methylphenidate-based NPS drugs including ethylphenidate were controlled by a TCDO; two additional methylphenidate-based NPS were added to the TCDO in June 2015 [21]. Methiopropamine was controlled by TCDO on 27 Nov 2015. The Psychoactive Substances Act (2016) came into effect on 26 May 2016, prohibiting the supply of any substance intended for human consumption capable of producing a psychoactive effect.

On 16 Oct 2015, trading standards officials obtained forfeiture orders for NPS from the Sheriff Court in Edinburgh, with the backing of Police Scotland [22]. This resulted in eight 'head shops' forfeiting their NPS supplies to the council.

Statistical analysis

We hypothesised before the methylphenidate TCDO that it might be associated with a change in the presentation of NPS patients to hospital; however, we used the null hypothesis for our formal statistical testing. The initial analysis was performed using Graphpad Prism v7; categorical variables were compared using chi-squared tests, continuous data with a two-tailed Mann Whitney test. However, this analysis could not account for underlying secular changes occurring before the interventions. There

was statistical evidence of over-dispersion in the Poisson regression models, and therefore we used negative binomial regression in Stat 14 (StataCorp, College Station, TX) to compare rates after the legislative (April 2015) and trading standard (October 2015) changes with those predicted based on pre-ban trends. We calculated rate ratios (and the change in the number of admissions) for each month compared to predicted rates based on extrapolated trends before the legislation (May 2014 to Mar 2015). Negative binomial regression models included a single trend term for calendar month and a dummy variable for each of the post-legislative months (21 dummy variables: Apr 2015 – Dec 2016). We could not estimate the effect on presentations because the highly variable numbers during the 12 months preceding the TCDO made it difficult to establish a baseline for the analysis.

Cost estimation

We estimated cost benefits from the reduced admissions from an NHS perspective using NHS financial year 2015–16 reference costs (HRG4) (<https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016>). For the cost of admissions, supplemental to presentations, we used the PA50Z [Ingestion poisoning] in-patient episode cost (£544.04).

RESULTS

Over the 33 months of this study, there were 4,513 presentations (median 137 [IQR 112 to 158] per month) and 1,912 admissions (median 61 [41 to 74] per month) to the Royal Infirmary of Edinburgh for recreational drug use. Of these, 935 (20.7%, median 26 [9 to 48] per month) presentations and 605 (31.6%, median 19 [4 to 31] per month) admissions were categorised as due to alleged NPS misuse.

Effect on NPS hospital presentations and admissions

The methylphenidate-based NPS TCDO (Apr 15) was associated with a rapid fall in presentations

(reduction of 46.7%, $p=0.002$) and admissions (reduction of 21.0%, $p=0.003$) for all NPS toxicity, comparing the twelve months before with the six months after the action (up to the trading standards action; figures 1 & 2, table 1). The median [IQR] number of ethylphenidate NPS admissions fell from 15 [13 to 18] per month before the TCDO to 1 [0 to 2] per month after, a reduction of 96.7% ($p<0.001$), while median monthly number of SCRA admissions tripled from 3 [2 to 5] before the TCDO to 10 [8 to 13] afterwards ($p<0.001$). There was no apparent replacement with conventional drugs (figure 1).

The trading standards activity (Oct 15) was associated with a further rapid reduction in all NPS presentations and admissions. Comparing the six months before the activity to the subsequent twelve months, the median monthly number of NPS presentations and admissions fell from 28.0 and 24.5 to 10.0 and 4.0 per month, falls of 64.3% ($p<0.001$) and 83.7% ($p<0.001$), respectively (table 1). The fall in presentations was sustained with medians of only 6.5 (IQR 3 to 11) and 2.5 (2 to 5) alleged NPS presentations and admissions per month, respectively, during the last six months of 2016 (figure 2).

Methiopropamine was not recognised to be a clinical problem in Edinburgh. Therefore, the TCDO (Nov 15) was not associated with any apparent effect on NPS admissions (figure 1).

The Psychoactive Substances Act (May 16) was associated with non-significant reductions in presentations and admissions for NPS toxicity: comparing the 6 months before with the 8 months after (until the end of 2016) revealed reductions of 6.3% ($p=0.591$) in presentations and 25.0% ($p=0.257$) in admissions (figures 1 & 2).

Effect on hospital presentations and admissions for conventional recreational drugs

It was difficult to detect any associated change in presentations for conventional recreational drug use immediately after each intervention, probably due to their rapid sequence. However, comparing the first

12 months of the study period (before the methylphenidate TCDO) with the last 12 months of the study period (starting 2 months after trading standards action), we found a significant increase (54.2%, $p=0.0103$) in conventional stimulant presentations but not admissions (table 2). By contrast, no significant effect in the number of presentations or admissions for conventional opioids, non-NPS benzodiazepines or unknown/other recreational drugs was seen (table 2). There was a small increase in admissions, but not presentations, for opioid toxicity in the three months immediately post methylphenidate TCDO that was not sustained (figure 2).

Looking at admissions for the different drug groups, there was little difference in the median age before the Apr 2015 intervention versus after the Oct 2015 intervention: NPS 33 yrs vs 32 yrs, $p=0.1209$; opioids 36 yrs vs 35 yrs, $p=0.8030$; non-NPS benzodiazepines 34 yrs vs 34 yrs, $p=0.8995$; classical stimulants 26 yrs vs 23 yrs, $p=0.0101$. There was no statistically significant change in the proportion of male to female patients after the interventions compared to the period before April 2015.

Deaths associated with recreational drugs

The interventions were associated with little effect on the number of deaths with any NPS detected, with 26 and 19 deaths in 2014 and 2016, respectively (figure 3). However, the number of ethylphenidate and methiopropamine post-mortem detections fell markedly, with 20 and 6 cases up to June 2015 versus none of either in 2016. Instead, the NPS detected in fatal cases during 2016 were novel benzodiazepines (etizolam 15, diclazepam 4). In contrast to the small fall in NPS detections, there were modest increases in detection of opioids (132 vs 171), classic stimulants (13 vs 36), and other drugs (61 vs 90) from 2014 to 2016. The number of cases with non-NPS benzodiazepines fell (146 vs 132).

Estimated effect of the methylphenidate TCDO and trading standards activity on admissions

Comparing the 12 months before the methylphenidate TCDO to the last 12 months of the study period, there were an estimated 557 (95%CI 327 to 934) fewer admissions than expected in 2016 if none of the interventions had occurred (43 compared to the expected 603). Using NHS costings for 2015-16, the interventions were associated with an estimated saving of £303,030 (95%CI £177,901 to £508,133) on admissions for NHS Lothian in Edinburgh during 2016.

DISCUSSION

Our study has shown an association between the methylphenidate-based NPS TCDO and a rapid and sustained fall in ethylphenidate related harms in Edinburgh. The fall in ethylphenidate admissions was soon followed by modestly increased use of SCRA. Subsequent trading standards activity to remove NPS from local shops was associated with a rapid reduction in all NPS presentations to hospital that was sustained for more than one year. This was associated with a 40% increase in presentations and admissions following classic stimulant use, but not opioids, non-NPS benzodiazepines, or other recreational drugs. The effect has now been sustained for 30 months (from Nov 2015 until now [May 2018]) with fewer than three NPS cases per month being admitted over the last six months (Pettie, unpublished results). This article adds to the existing modest evidence for the effect of public health NPS interventions [9, 12].

The reduction associated with the TCDO and trading standards action was surprising since NPS are widely available on the web and it was presumed that sales and use would continue from the web after removal of NPS drugs from local shops [13, 23]. That this did not appear to happen instead suggests that the use of these drugs, at least in Edinburgh, was driven by sales of NPS in local shops, not via the web. Discussions with our patients and with colleagues in public health suggested that the life of some NPS users was too chaotic for them to use web-based sales and that easy access drove new users to

272 NPS drugs who did not then continue to use them when access became more difficult. Despite
273 previous evidence [18, 19] that heroin users were attracted to NPS use by their availability, there was
274 no marked increase in the number of hospital admissions or in deaths from opioid toxicity in the period
275 following the interventions as might have occurred if users went back to their usual doses of heroin for
276 which they had lost tolerance, as predicted might occur (<http://www.nedac.co.uk/news.htm>).

277

278 There have been no previous reported studies looking in general at the association of trading standard
279 activity or TCDOs on presentations to hospital with NPS toxicity in the UK. One study looking at the
280 number of phone calls and TOXBASE accesses for methoxetamine after its TCDO in April 2012, noting
281 a marked fall in the following months [24]. Retrospective studies in Edinburgh found a reduction in
282 *Streptococcus pyogenes* and *Staphylococcus aureus* skin infections [25], and lower reported use of
283 ethylphenidate by psychiatric patients [26], after the TCDO and trading standards action. A
284 comprehensive review of the international literature to 2016 reported a series of methodologically weak
285 studies presenting similar before and after data for bans of particular NPS [12]. These studies all
286 showed a general decline in incidence after bans [12]. Unfortunately, the difficulty of performing a
287 randomised controlled study of a public health intervention for NPS control limits the ability to produce
288 high quality effectiveness data.

289

290 Our data suggest that trading standards enforcement may be particularly effective at sustainably
291 reducing NPS use and harms. Implementing trading standards actions across the country, if productive
292 of similar effects, may reduce direct hospital costs by millions of pounds. It was not possible to look at
293 the effects of the Psychoactive Substances Act because the rate of NPS drug presentations/admissions
294 had already fallen by May 2016 to low levels following the TCDO and trading standards activity. Any
295 associated effect of the methiopropamine TCDO could not be detected because, although found post-
296 mortem for six Edinburgh cases in 2014-15, it was not recognised as a clinical problem and therefore

297 not recorded in the hospital database.

298

299 This paper is limited by the data being from only one hospital in one part of the UK. Edinburgh has
300 been badly hit by NPS toxicity over the last decade, with the very large numbers of ethylphenidate
301 cases being specifically recognised in the text of the methylphenidate TCDO [21]. Prospective audit of
302 admitted patients provided data from before and after the actions to be compared using identical
303 methodology. Admission of patients to one of the UK's specialist toxicology wards meant that effort was
304 made to identify the drug involved from history, clinical syndrome, and knowledge of local epidemiology
305 (from police seizures and laboratory analysis). However, anonymous collection of routine audit data did
306 not allow for collection of data on co-morbidity, particularly psychiatric history.

307

308 However, a second limitation is the lack of laboratory proven identification of the drug involved for each
309 patient. Since identification of the drug would not have assisted clinical management, and the
310 turnaround for analysis too long to be clinically useful, such analysis would have required setting up a
311 research study and seeking funds for the analysis - both of which would have taken time and hindered
312 the collection of prospective data before the first intervention. Although the precise recreational drug
313 involved cannot be identified for sure, there were clear changes in the toxidromes of patients presenting
314 over time consistent with the switch from ethylphenidate to SCRA, and then away from SCRA.
315 Furthermore, the interventions were associated with a near complete reduction in all cases of NPS
316 toxicity, making the identification of the responsible compounds moot. The history-based data from the
317 clinical cases were similar to the forensic toxicology analysis-derived data being performed on patients
318 dying from suspected overdose in Edinburgh.

319

320 A third limitation was the short interval between actions, with several interventions following each other
321 in quick succession, reducing the amount of data between interventions available with which to analyse

associated effects. The periods between interventions also varied meaning that we had to use different duration data for comparisons. Since we preferred to use all the data available, we did not drop data to make the durations of similar length. The constantly changing epidemiology of NPS drug use also meant that it was difficult to identify a baseline or underlying secular change for presentations before the first intervention.

In conclusion, TCDOs and trading standards activity were associated with a remarkable and sustained reduction in the number of presentations and admissions for NPS toxicity in Edinburgh. If causal, such actions implemented across the UK may be able to turn the tide against these highly damaging drugs. It seems unlikely that controlled public health studies will occur in the future; further observational studies may provide more data on the possible causal relationship between such interventions and reducing harm from NPS.

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CONFLICTS OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article

DETAILS OF CONTRIBUTORS

JP, MD and JD set up the prospective database of recreational drug patients. JP, AB, MD, KO, RG, DS,

347 and KE extracted the data. HT extracted the forensic toxicology data. ME and DK analysed the data.

348 ME wrote the first draft of the paper; all authors then critically revised it.

349

350 ME is the guarantor for the study. He had full access to all of the data in the study and can take

351 responsibility for the integrity of the data and the accuracy of the data analysis.

352

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432

433

TABLE 1
Changes in median (IQR) monthly admissions and presentations for NPS drug toxicity, related to interventions

NPS		Pre	Post	P value
TCDO Apr 15		Apr 2014 to Mar 2015	Apr 2015 to Sept 2015	
	Presentations	52.5 [42 to 58] (n=12)	28 [24 to 34] (n=6)	p=0.002
	Admissions	31 [29 to 37] (n=12)	24.5 [18 to 28] (n=6)	p=0.003
Trading standards Oct 15		Apr 2015 to Sept 2015	Oct 2015 to Sept 2016	
	Presentations	28 [24 to 34] (n=6)	10 [6 to 15] (n=12)	P<0.001
	Admissions	24.5 [18 to 28] (n=6)	4 [3 to 5] (n=12)	P<0.001
PSA May 16		Nov 2015 to Apr 2016	May 2016 to Dec 2016	
	Presentations	8 [6 to 16] (n=6)	7.5 [5 to 12] (n=8)	p=0.591
	Admissions	4 [3 to 5] (n=6)	3 [2 to 5] (n=8)	p=0.257

Abbreviations: PSA, Psychoactive Substances Act; TCDO, temporary class drug order

TABLE 2

Changes in median (IQR) monthly admissions and presentations for non-NPS drug toxicity for the 12 months before the methylphenidate TCDO (Apr 2014 to Mar 2015) and 12 months of 2016 (Jan to Dec 2016)

Drug class		Pre	Post	P value
Conventional opioids	Presentations	32.5 [26 to 40] (n=12)	31 [23 to 37] (n=12)	p=0.560
	Admissions	17 [15 to 23] (n=12)	13.5 [12 to 22] (n=12)	p=0.282
Conventional stimulants	Presentations	24 [21 to 31] (n=12)	37 [26 to 39] (n=12)	p=0.010
	Admissions	7.5 [3 to 8] (n=12)	8.5 [5 to 10] (n=12)	p=0.294
Non-NPS benzodiazepines	Presentations	15.5 [12 to 19] (n=12)	16.5 [14 to 22] (n=12)	p=0.433
	Admissions	8 [7 to 9] (n=12)	7.5 [6 to 10] (n=12)	p=0.743
Other/unknown	Presentations	29.5 [26 to 30] (n=12)	31 [28 to 39] (n=12)	p=0.153
	Admissions	5.5 [2 to 8] (n=12)	7 [5 to 9] (n=12)	p=0.160

FIGURE LEGENDS

Figure 1. Numbers of presentations (top) and admissions (bottom) with recreational drug toxicity to the Royal Infirmary of Edinburgh between April 2014 and December 2016, related to recreational drug legislation and trading standard enforcement.

All NPS are grouped together in the presentations section (top). In the admissions section, where the NPS used was sub-classified by clinical examination and careful history taking, NPS are further subdivided into NPS stimulants (such as ethylphenidate) and NPS SCRA's.

The number of all NPS admissions fell sharply in April 2015 after the ethylphenidate TCDO and again in Oct 2015 after the trading standards action. Review of the admissions data show that the initial fall was due to an almost complete reduction in stimulant NPS admissions. The stimulant NPS were replaced by NPS SCRA admissions for six months before these too were markedly reduced after Oct 2015.

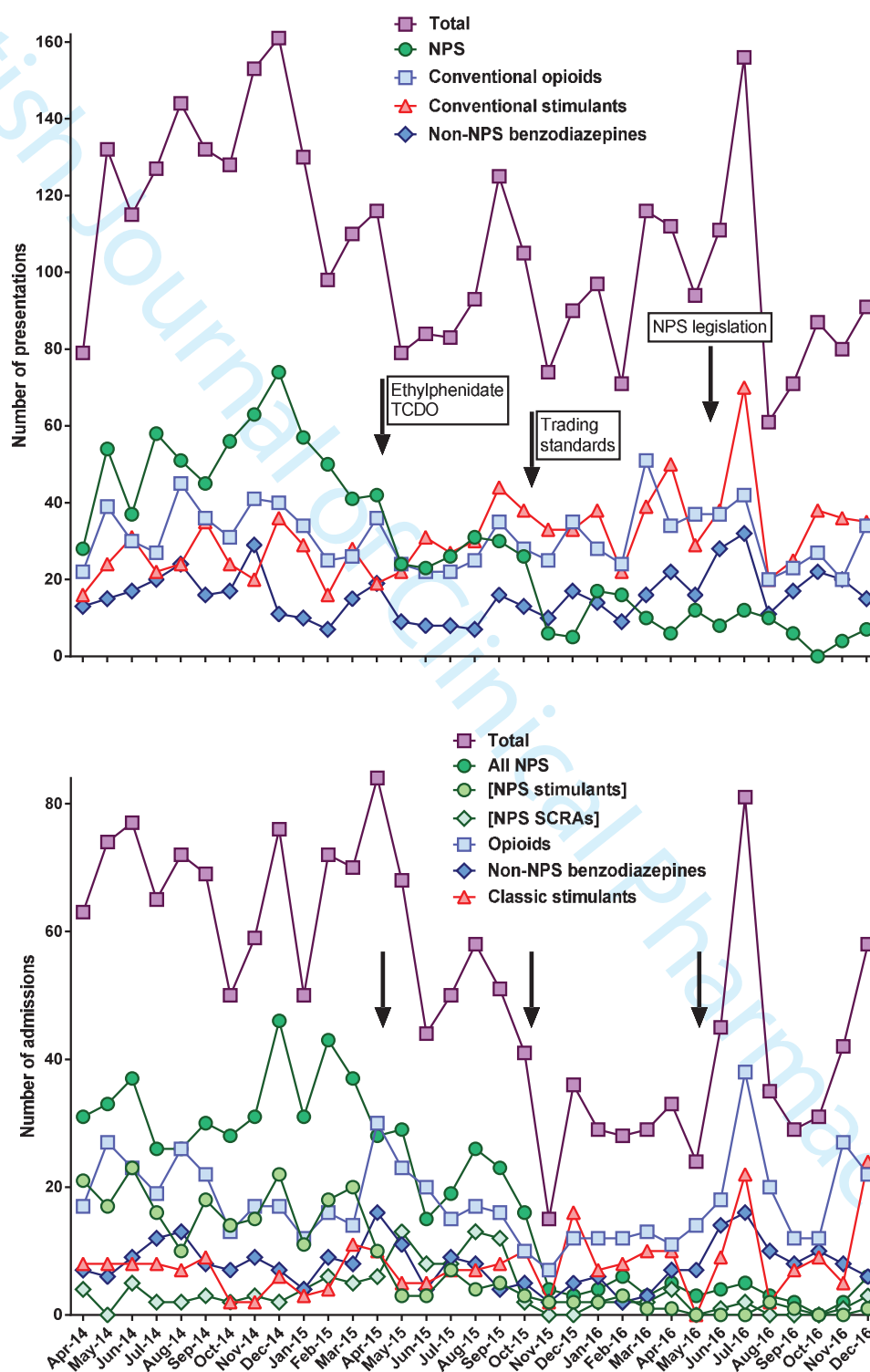
Figure 2. Numbers of admissions with NPS toxicity to the Royal Infirmary of Edinburgh between April 2014 and December 2016.

In this figure, the NPS admissions are broken down into further subsections showing the initial high number of NPS ethylphenidate and NPS unknown (likely ethylphenidate) admissions.

Abbreviations: NPS total: all admissions with NPS toxicity; NPS E: ethylphenidate; NPS Uk: unknown NPS drug; NPS SC: SCRA; NPS Stim: stimulant NPS (not ethylphenidate); NPS Sed: sedative NPS; NPS Hall: hallucinogenic NPS.

Figure 3. Number of deaths in Edinburgh region with recreational drugs detected in plasma or urine analysis by quarter.

475 Figure 1



476

Figure 2

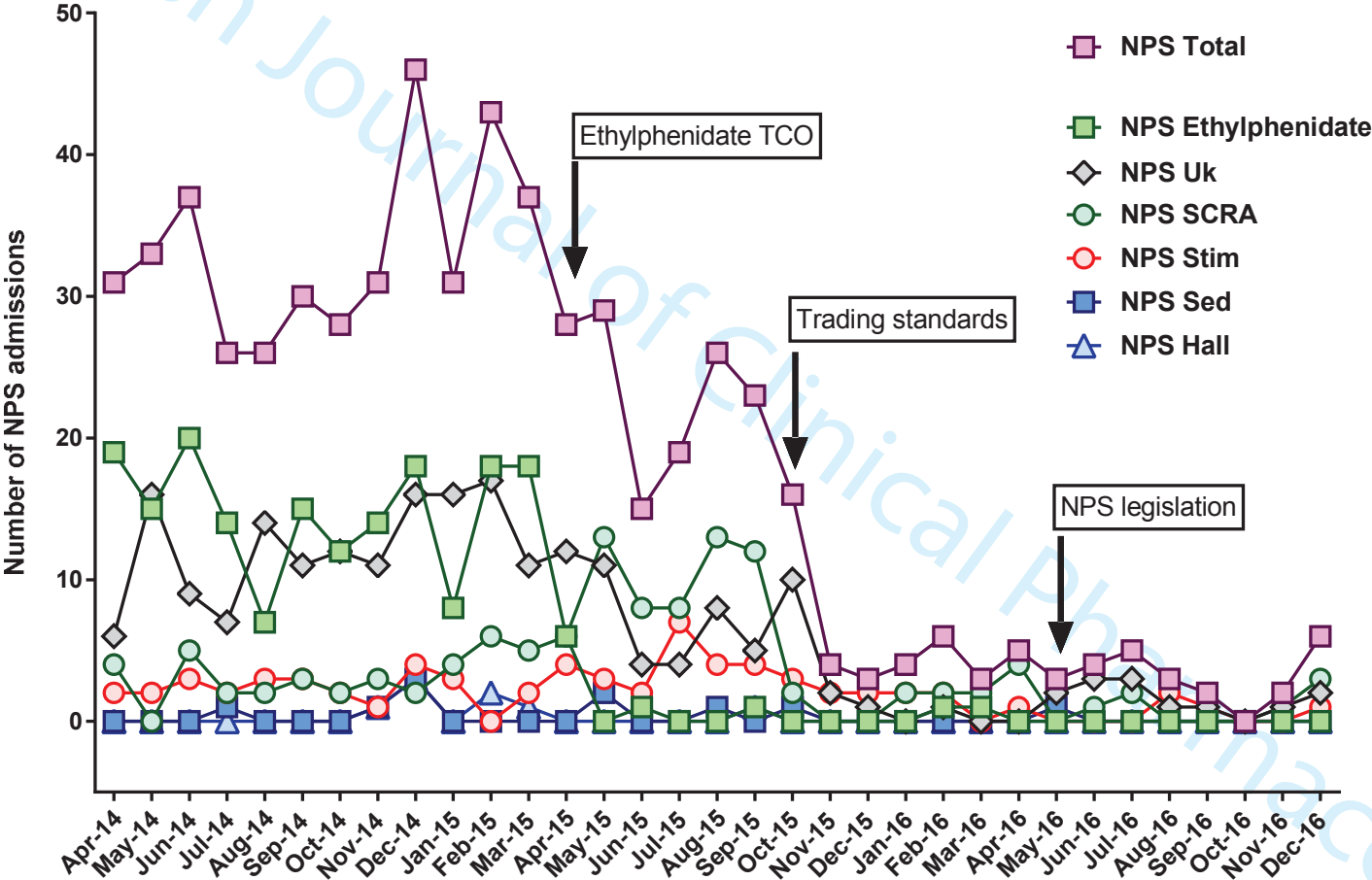


Figure 3

